DEPARTMENT OF **HEALTH** & HUMAN SERVICES

HFD-613

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-20 l/S-O09

FEB 1 7 1999

Abbott Laboratories
Hospital Products Division
Attention: Ms. Jean Conaway
D-389, Bldg. AP 30
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Conaway:

Please refer to your supplemental new drug application dated February 16, 1996 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dobutamine in 5% Dextrose Injection in CR3 Flexible Containers.

We acknowledge receipt of your submission dated January 22, 1999.

This supplemental new drug application, as amended, provides for draft labeling revised to add information relating to the dosing of these products in the pediatric population. In addition, the **INDICATIONS AND USAGE** section has been revised to provide for updated information relating to maximum duration of treatment.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling included with your January 22, 1999 submission with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

As discussed by telephone on February 4, 1999 between Ms. Leslie Koehler and Mr. Gary Buehler, the words "adults with" should be deleted from the third line of the **INDICATIONS AND USAGE** section of the labeling.

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3 14.80 and 314.81.

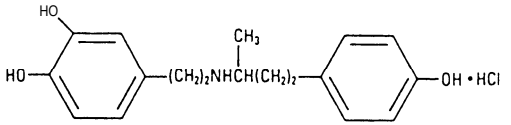
DOBUTAMINE
in 5% Dextrose Injection
Flexible Plastic Container

DESCRIPTION

Dobutamine in 5% Dextrose injection is a sterile, nonpyrogenic, prediluted solution of dobutamine hydrochloride and dextrose in water for injection. It is administered by intravenous infusion.

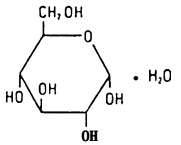
Each 100 mL contains dobutamine hydrochloride equivalent to 50 mg, 100 mg, 200 mg, or 400 mg of dobutamine; dextrose, hydrous 5 g in water for injection, with sodium metabisulfite 25 mg and edetate disodium, dihydrate 10 mg added as stabilizers; osmolar concentration, respectively, 260, 263, 270, or 284 mOsmol/liter (calc). The pH is 3.0 (2.5 to 5.5). May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. Dobutamine in 5% Dextrose Injection is oxygen sensitive.

Dobutamine Hydrochloride, USP is chemically designated (±)-4-[2-[[3-(p-hydroxyphenyl)-1 -methylpropyl]amino]ethyl]-pyrocatechol hydrochloride. It is a synthetic catecholamine.



Molecular Formula: $C_{18}H_{23}NO_3 \cdot HCl$ Molecular Weight: 337.85

Dextrose, USP is chemically designated D-glucose monohydrate ($C_6H_{12}O_6 \cdot H_2O$), a hexose sugar freely soluble in water. It has the following structural formula:



Water for Injection, USP is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the p-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term, not more than several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of dobutamine in 5% dextrose injection is within 1 to 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is 2 minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-0 methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

The effective infusion rate of dobutamine varies widely from patient to patient, and titration is always necessary (see DOSAGE AND ADMINISTRATION). At least in pediatric patients, dobutamine-induced increases in cardiac output and systemic pressure are generally seen, in any given patient, at lower infusion rates than those that cause substantial tachycardia. (See Pediatric Use under PRECAUTIONS)

INDICATIONS AND USAGE

Dobutamine in 5% Dextrose injection is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures. Experience with intravenous dobutamine in controlled trials does not extend beyond 48 hours of repeated boluses and/or continuous infusions.

Whether given orally, continuously intravenously, or intermittently intravenously, neither dobutamine nor any other cyclic-AMP-dependent inotrope has been shown in controlled trials to be safe or effective in the long-term treatment of congestive heart failure. In controlled trials of chronic oral therapy with various such agents, symptoms were not consistently alleviated, and the cyclic-AMP-dependent inotropes were consistently associated with increased risks of hospitalization and death. Patients with NYHA Class IV symptoms appeared to be at particular risk.

CONTRAINDICATIONS

Dobutamine in 5% Dextrose Injection is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine.

Dextrose solutions without electrolytes should not be administered simultaneously with blood through the same infusion set because of the possibility that pseudoagglutination of red cells may occur.

WARNINGS

1. Increase in Heart Rate or Blood Pressure

Dobutamine hydrochloride may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of adult patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage promptly reverses these effects.

Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. In patients who have atrial fibrillation with

rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine. Patients with pre-existing hypertension appear to face an increased risk of developing an exaggerated pressure response.

2. Ectopic Activity
Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. Hypersensitivity
Reactions suggestive of hypersensitivity associated with administration of dobutamine in 5% Dextrose Injection, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

Additive medications should not be delivered via this solution.

4. Dobutamine in 5% Dextrose Injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

1. During the administration of dobutamine, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutamine in 5% Dextrose Injection.
2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutamine in *5%* Dextrose Injection is instituted.
3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a p-blocking drug. In such a case, the peripheral vascular resistance may increase.
4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.
5. Dobutamine, like other P-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.
6. Excess administration of potassium-free solutions may result in significant hypokalemia.

The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

7. Avoid bolus administration of the drug. See DOSAGE AND ADMINISTRATION.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

8. Dobutamine in 5% Dextrose Injection may exhibit a pink color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the time of administration. Do not administer unless solution is clear and container is undamaged. Discard unused portion.

Usage Following Acute Myocardial Infarction: **Clinical experience with dobutamine following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.**

Carcinogenesis, Mutagenesis, Impairment of Fertility**: Studies to evaluate the carcinogenic or mutagenic potential of dobutamine or the potential of the drug to affect fertility adversely have not been performed.**

Pregnancy

Pregnancy Category B: **Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to dobutamine. The drug, however, has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.**

Pediatric Use: **Dobutamine has been shown to increase cardiac output and systemic pressure in pediatric patients of every age group. In premature neonates, however, dobutamine is less effective than dopamine in raising systemic blood pressure without causing undue tachycardia, and dobutamine has not been shown to provide any added benefit when given to such infants already receiving optimal infusions of dopamine.**

Drug Interactions: **There was no evidence of drug interactions in clinical studies in which dobutamine hydrochloride was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.**

ADVERSE REACTIONS

Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity: **A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of *5* to 15 beats/minute have been noted in most patients (see WARNINGS regarding exaggerated chronotropic and pressor effects). Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.**

Hypotension: **Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate.**

Reactions at Sites of Intravenous Infusion: **Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration.**

Miscellaneous Uncommon Effects: **The following adverse effects have been reported in 1% to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.**

Administration of dobutamine, like other catecholamines, has been associated with decreases in serum potassium concentrations, rarely to hypokalemic levels (See PRECAUTIONS).

OVERDOSAGE

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.

Signs and Symptoms: **Toxicity from dobutamine hydrochloride is usually due to excessive cardiac B-receptor stimulation. The duration of action of Dobutamine hydrochloride is generally short ($T_{1/2}$ = 2 minutes) because it is rapidly metabolized by catechol-O-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, and anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of Dobutamine on the myocardium may cause hypertension, tachyarrhythmias, myocardial ischemia, and ventricular fibrillation. Hypotension may result from vasodilation.**

If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract,

Treatment: **To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' *Desk Reference (PDR).* In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.**

The initial actions to be taken in a dobutamine hydrochloride overdose are discontinuing administration, establishing an airway, and ensuring oxygenation and ventilation. Resuscitative measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lidocaine. Hypertension usually responds to a reduction in dose or discontinuation of therapy.

Protect the patient's airway and support ventilation and perfusion. If needed, meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage: consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.

DOSAGE AND ADMINISTRATION

Do NOT add sodium bicarbonate or other alkalinizing substance, since dobutamine is inactivated in alkaline solution. Dobutamine in 5% Dextrose Injection is administered only intravenously via a suitable catheter or needle infusion. The less concentrated 0.5 mg/mL solution may be preferred when fluid expansion is not a problem. The more concentrated 1 mg/mL, 2 mg/mL, or 4 mg/mL solutions may be preferred in patients with fluid retention or when a slower rate of infusion is desired.

Recommended Dosage: **infusion of dobutamine should be started at a low rate (0.5 to 1.0 mcg/kg/min) and titrated at intervals of a few minutes, guided by the patient's response, including systemic blood pressure, urine flow, frequency of ectopic activity, heart rate, and (whenever possible) measurements of cardiac output, central venous pressure, and/or pulmonary capillary wedge pressure. In reported trials, the optimal infusion rates have varied from patient to patient, usually 2 to 20 mcg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect. For the infusion rates necessary to achieve various delivery rates mcg/kg/min) for patients of different weights, refer to the Dobutamine Infusion Rate (mL/hr) charts below.**

Rate of Administration: **When administering dobutamine (or any potent medication) by continuous intravenous infusion, it is advisable to use a precision volume control I.V. set.**

Each patient must be individually titrated to the desired hemodynamic response to dobutamine. The rate of administration and the duration of therapy should be adjusted according to the patient's response as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

As with all potent intravenously administered drugs, care should be taken to control the rate of infusion so as to avoid inadvertent administration of a bolus of the drug.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit (see PRECAUTIONS).

Dobutamine Infusion Rate (mL/hr) Chart Using 500 mcg/mL Concentration

	Patient Body Weight (kg)												
Infusion rate (mcg/kg/min)	5	10	20	30	40	50	60	70	80	90	100	110	120
2.5	1.5	3	6	9	12	15	18	21	24	27	30	33	36
5	3	6	12	18	24	30	36	42	48	54	60	66	72
7.5	4.5	9	18	27	36	45	54	63	72	81	90	99	108
10	6	12	24	36	48	60	72	84	96	108	120	132	144
12.5	7.5	15	30	45	60	75	90	105	120	135	150	165	180
15	9	18	36	54	72	90	108	126	144	162	180	198	216
17.5	10.5	21	42	63	84	105	126	147	168	189	210	231	252

Dobutamine Infusion Rate (mL/hr) Chart Using 1000 mcg/mL Concentration

	Patient Body Weight (kg)												
Infusion rate (mcg/kg/min)	5	10	20	30	40	50	60	70	80	90	100	110	120
2.5	0.75	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
5	1.5	3	6	9	12	15	18	21	24	27	30	33	36
7.5	2.25	4.5	9	13.5	18	22.5	27	31.5	36	40.5	45	49.5	54
10	3	6	12	18	24	30	36	42	48	54	60	66	72
12.5	3.75	7.5	15	22.5	30	37.5	45	52.5	60	67.5	75	82.5	90
15	4.5	9	18	27	36	45	54	63	72	81	90	99	108
17.5	5.25	10.5	21	31.5	42	52.5	63	73.5	84	94.5	105	115.5	126

Dobutamine Infusion Rate (mL/hr) Chart
Using 2000 mcg/mL Concentration

	Patient Body Weight (kg)									
Infusion rate (mcg/kg/min)	30	40	50	60	70	80	90	100	110	120
2.5	2.25	3	3.75	4.5	5.25	6	6.75	7.5	8.25	9
5	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
7.5	6.75	9	11.25	13.5	15.75	18	20.25	22.5	24.75	27
10	9	12	15	18	21	24	27	30	33	36
12.5	11.25	15	18.75	22.5	26.25	30	33.75	37.5	41.25	45
15	13.5	18	22.5	27	31.5	36	40.5	45	49.5	54
17.5	15.75	21	26.25	31.5	36.75	42	47.25	52.5	57.75	63

Dobutamine Infusion Rate (ml/hr) Chart
Using 4000 mcg/mL Concentration

	Patient Body Weight (kg)									
Infusion rate (mcglkglmin)	30	40	50	60	70	80	90	100	110	120
2.5	1.125	1.5	1.875	2.25	2.625	3	3.375	3.75	4.125	4.5
5	2.25	3	3.75	4.5	5.25	6	6.75	7.5	8.25	9
7.5	3.375	4.5	5.625	6.75	7.875	9	10.125	11.25	12.375	13.5
10	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
12.5	5.625	7.5	9.375	11.25	13.125	15	16.875	18.75	20.625	22.5
15	6.75	9	11.25	13.5	15.75	18	20.25	22.5	24.75	27
17.5	7.875	10.5	13.125	15.75	18.375	21	23.625	26.25	28.875	31.5

INSTRUCTIONS FOR USE

To Open

Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Preparation for Administration

(Use aseptic technique)

1. **Close flow control clamp of administration set**
2. **Remove cover from outlet port at bottom of container.**
3. **Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. NOTE: See full directions on administration set carton.**
4. **Suspend container from hanger.**
5. **Squeeze and release drip chamber to establish proper fluid level in chamber.**
6. **Open flow control clamp and clear air from set. Close clamp.**
7. **Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.**

a. **Regulate rate of administration with flow control clamp.**

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Dobutamine in 5% Dextrose Injection is supplied in 250 and 500 mL LifeCare flexible containers as follows:

List No. 2345 – 125 mg Dobutamine in 5% Dextrose Injection 250 mL
List No. 2345 – 250 mg Dobutamine in 5% Dextrose Injection 500 mL
List No. 2346 – 256 mg Dobutamine in 5% Dextrose Injection 250 mL
List No. 2346 – 500 mg Dobutamine in 5% Dextrose Injection 500 mL
List No. 2347 – 500 mg Dobutamine in 5% Dextrose Injection 250 mL
List No. 3724 – 1000 mg Dobutamine in 5% Dextrose Injection 250 mL

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product

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